THE ROLE OF THE VIRAL NEF PROTEIN AS A MEDIATOR OF HIV-1 INDUCED ENDOTHELIAL DYSFUNTION

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With the prevalence of antiviral therapy in the developed world, many HIV-1-infected people die of diseases other than AIDS. One of the emerging major causes is cardiovascular disease, leading to the prediction that the majority of HIV-1 patients are expected to develop cardiovascular complications. Endothelial dysfunction is thought to be a key event in the development of cardiovascular diseases, particularly atherosclerosis. Assays testing the effect of HIV-1 on endothelial activation shows that direct contact with HIV-1 infected T cells enhance endothelial cell activation to a greater extent than HIV-1 alone, suggesting an intracellular HIV-1 protein is responsible for endothelial activation. The HIV-1 viral protein Nef, which is responsible for T cell activation and maintenance of high viral loads *in vivo*, has been shown to mediate its own transfer to bystander cells. We demonstrate here for the first time that Nef induces nanotube-like conduits connecting T cells and endothelial cells. We also show that Nef is transferred from T cells to endothelial cells via these nanotubes, and is necessary and sufficient for endothelial cell activation. Moreover, we show that SIV-infected macaques exhibit endothelial Nef expression in coronary arteries. Nef expression in endothelial cells causes endothelial apoptosis, ROS and MCP-1 production. Interestingly, a Nef SH3 binding site mutant abolishes Nef-induced apoptosis and ROS formation and reduces MCP-1 production in endothelial cells, suggesting that the Nef SH3 binding site is critical for Nef effects on endothelial cells. Nef induces apoptosis of endothelial cells through an NADPH oxidase- and ROS-dependent mechanism, while Nef-induced MCP-1 production is NF-kB dependent. Taken together, these data suggest that Nef can mediate its transfer from T cells to endothelial cells through nanotubes to enhance endothelial dysfunction *in vivo.* Thus, Nef is a promising new therapeutic target for reducing the risk for cardiovascular disease in the HIV-1 positive population.